Pharmacogenetics of Codeine

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Codeine Overview

- Naturally occurring opium alkaloid
- Demethylated to morphine for analgesic effect
- Less potent than morphine (affinity for μ-opioid receptor 200-fold weaker)
- Used for relief of mild to moderately severe pain
- Usual oral dose
  - Children: 0.5mg/kg every 4-6 hours as needed
  - Adults: 15-60mg every 4 hours as needed
- In combination with acetaminophen, FDA approved in patients 3 years and older

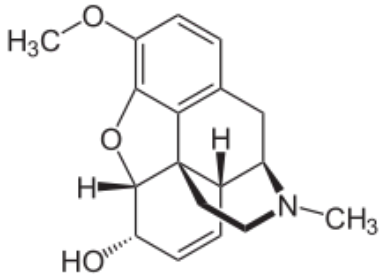
Codeine Adverse Events

- Common adverse events (AEs)
  - Drowsiness, dizziness, sedation, shortness of breath, nausea and vomiting
- Other AEs
  - Euphoria, dysphoria, allergic reactions, constipation
- AEs at high doses
  - Most of the disadvantages of morphine including respiratory depression

Codeine Pharmacokinetics

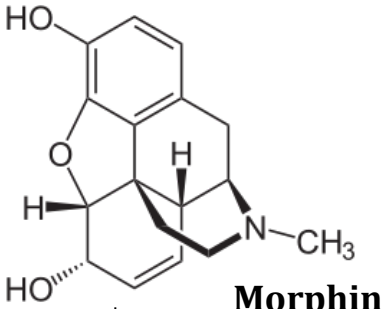
- Absorption
  - Readily absorbed from GI tract
- Distribution
  - Distributes to liver, spleen, and kidney
  - Crosses blood-brain barrier
  - Excreted in breast milk
- Metabolism and Elimination
  - Primary hepatic clearance (UGT2B7, CYP3A4, and CYP2D6)
  - t1/2: 2.9 hours
  - Renal excretion (parent and metabolites)
  - Plasma concentration does not correlate with CNS concentration or relief of pain

Codeine Metabolism



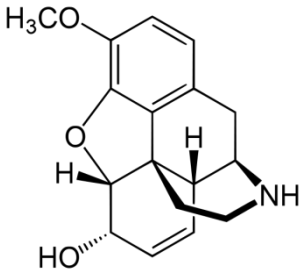
codeine
(inactive)

CYP2D6
(5-15%)



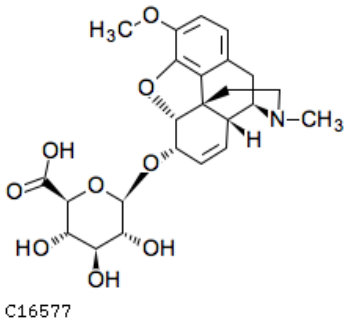
Morphine
(active)

CYP3A4
(10-20%)



norcodeine
(inactive)

Glucuronidation
(60-70%)



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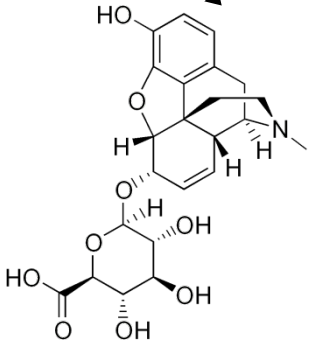
Codeine 6 glucuronide
(inactive)

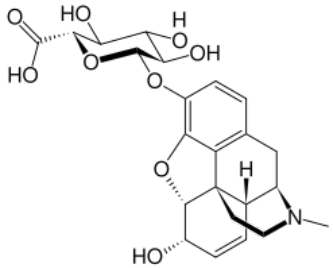
Glucuronidation

15%



Morphine 6 glucuronide
(active but does not cross BBB)

50%



Morphine 3
glucuronide
(inactive)

CYP2D6 Pharmacogenetics

Phenotype	Prevalence	Genotype
Poor metabolizer (PM)	5-10%	2 non-functional alleles
Intermediate metabolizer (IM)	2-11%	1 reduced and 1 non-functional allele
Extensive metabolizer (EM)	77-92%	2 functional or reduced function alleles, or 1 functional with a non-functional or reduced function allele
Ultra-rapid metabolizer (UM)	1-2%	More than two functional alleles

- > 80 allele variations, each with different effects
- Phenotype based on functional impact
- Enzymatic activity range from entirely absent (PM) to substantially higher than average (UM)

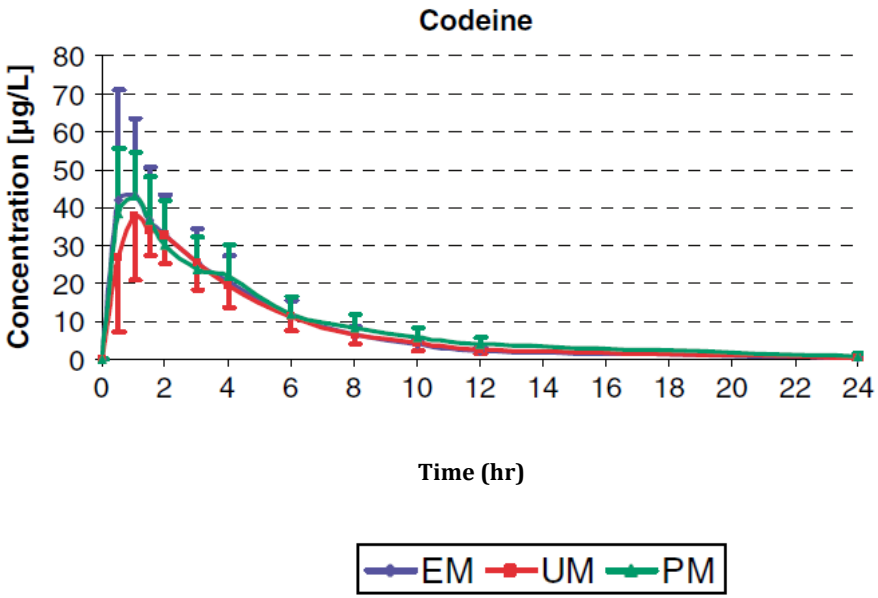
Crews KR et Al. *Clinical Pharmacology and Therapeutics*. February 2012

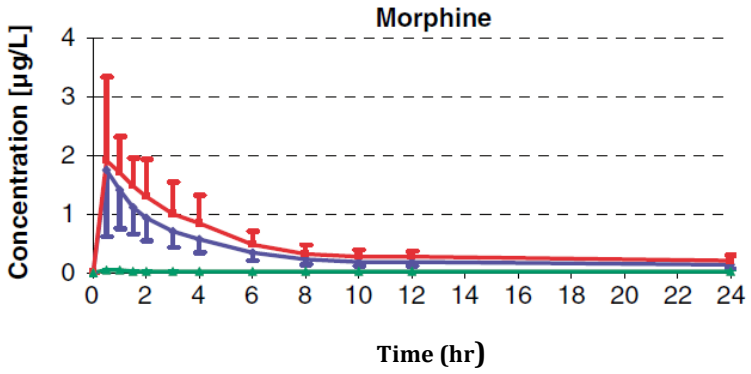
Rates of Genetic Polymorphisms Vary by Race and Ethnicity

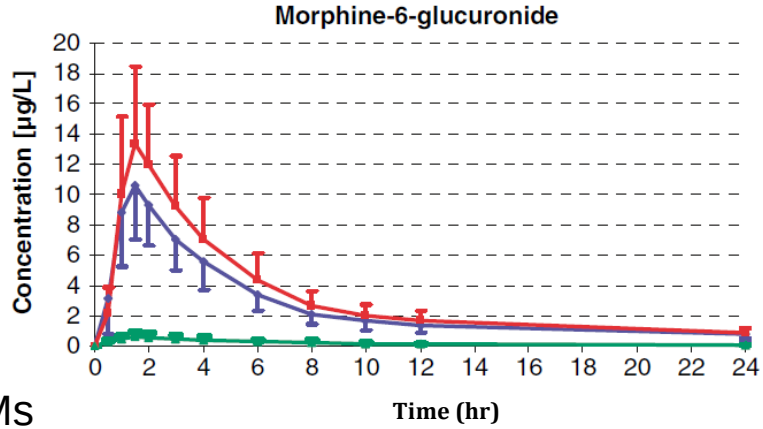
Population	UM Genotypes/Phenotypes (↑ Activity)	Prevalence % (UM/Total n)
African/Ethiopian[4]	UM (active duplicate genes)	29% (35/122)
African American[5, 6]	UM (three active duplicate genes)	3.4% (3/87) 6.5% (60/919)
Asian[7, 8, 9]	UM (active duplicate genes)	1.2% (5/400) 2%
Caucasian[5, 6]	UM (three active duplicate genes)	3.6% (33/919) 6.5% (18/275)
Greek[10]	CYP2D6*2xN/UM	6.0% (17/283)
Hungarian[11]	UM (active duplicate genes)	1.9%
Northern European[10, 12]	UM (active duplicate genes)	1-2%

FDA Drug Safety Communication. Codeine. 2012

CYP2D6 Polymorphisms Alter Morphine Exposure





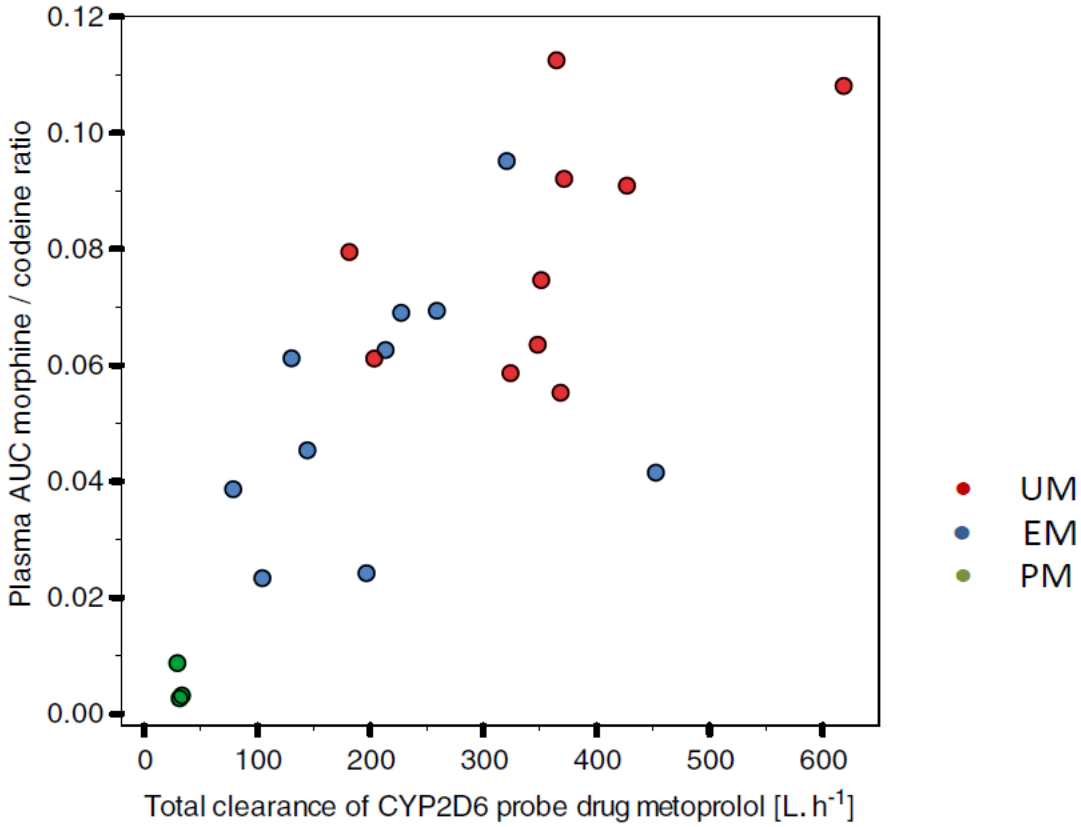


CYP2D6 polymorphisms

- Increased conversion of codeine to morphine in UMs
  - *Higher risk of toxicity in 1-2% of patients*
- Greatly reduced morphine formation following codeine administration in PMs
  - *Codeine may be ineffective in 5-10% of patients*

Kirchheiner J et al. *The Pharmacogenomics Journal* 2007.

Morphine Concentrations In EMs and UMs Are Highly Variable and Overlap



Kirchheiner J et al. *The Pharmacogenomics Journal* 2007.

CYP2D6 Polymorphisms Alter Codeine Effects

- Several studies have documented lack of analgesic effect in PMs
- Several case reports of severe or life-threatening side effects in UMs
- Case reports of morphine toxicity in breastfed infants of UM mothers
  - Product label changed to include warning
- Case report of morphine toxicity in UM adult also taking CYP3A4 inhibitor

Opioid Metabolism

Drug	Analgesic activity of product	Active metabolite (opioid agonist)	Non-active metabolites
Codeine	Metabolite	CYP2D6 (~10%): morphine	glucuronidation CYP3A4
Hydrocodone	Parent and metabolite	CYP2D6 (~14%): hydromorphone	CYP3A4
Oxycodone	Parent (metabolite?)	CYP3A4 (~60%): noroxycodone—weak analgesic CYP2D6 (~11%): oxymorphone	
Tramadol	Parent and metabolite	CYP2D6: O-desmethyltramadol	CYP3A4 CYP2B6
Morphine	Parent	Glucuronidation (UGTB7): M6G	Glucuronidation

Summary

- Following recommended doses of codeine:
  - UMs have increased formation of morphine increasing the risk for toxicity
  - PMs have greatly reduced morphine formation resulting in ineffective analgesia
- The prevalence of UMs is high in some populations

Thank you!